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Differential Distribution of Langerhans Cells in Organ Culture of Human Skin

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Epidermal Langerhans cells (LCs) function as the antigen-presenting cells in such cutaneous cell-mediated immune responses as contact hypersensitivity and in the mixed epidermal cell-lymphocyte reaction. They have also been implicated in the immune response in skin allograft rejection. Since organ culture of thyroid and pancreas has been shown to prolong allograft survival, presumably through the loss of antigen-presenting cells, we examined the effect of skin explant culture on LC survival. Human skin explants were placed in organ culture and examined serially as whole mounts of epidermis for the presence of LCs as judged by ATPase activity, and OKT-6 and HLA-DR antigens. Although we observed morphologic changes and an absolute reduction in the number of positively stained cells, culture for up to 28 days failed to deplete explants of these cells. Langerhans cells were also sought in the epidermal outgrowths that develop peripheral to the original explants. They were never seen in the area beyond 0.3 mm from the explant edge. Organ culture of skin thus provides a means to explore the contribution of LCs to skin allograft rejection by comparing the immunogenicity of epidermal portions of the explant with the epidermal outgrowth.

It has been postulated that the presence of a subpopulation of bone marrow-derived cells probably of macrophage/monocyte lineage is required for the activation of T lymphocytes in immune responses [1]. Termed dendritic cells because of their distinct morphology, these cells have been described in a wide variety of tissues including the spleen, lymph node [2], thymus [3], kidney [4], and heart [5]. Epidermal Langerhans cells (LCs) have been shown to have morphologic and phenotypic properties similar to dendritic cells [6]. They, too, originate in the bone marrow [7,8], are the only epidermal cells to possess C3 and Fc surface membrane receptors [9], and bear large quantities of class II (Ia-like, HLA-D/DR in humans) alloantigens [10–12]. Functionally, LCs, like dendritic cells, have been implicated in initiating the immune response to antigen in contact hypersensitivity [13–15], in the mixed epidermal cell-lymphocyte reaction [16], and in certain viral disorders [17]. Langerhans cells also contribute to the immunogenicity of keratinizing tissue in allograft reactions [18,19].

Because organ culture of such tissues as the thyroid [20], pancreas [21], and ovary [22] increases allograft survival, presumably through the loss of Ia-bearing, antigen-presenting cells, it was of interest to observe the effect of prolonged culture of skin on the morphology and numbers of LCs in human skin explants as well as in the outgrowth of epidermis that arises peripheral to the explant.

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Abbreviations:
LC: Langerhans cell

MATERIALS AND METHODS

Skin Tissue and Culture Techniques

Human skin was obtained from 8 adult women undergoing reduction mammoplasty. Explants were prepared within 24 hr of the surgical procedure using a modification of the technique of Halprin et al [23]. Using a Castroviejo keratome set at 0.2 mm, thin sheets of skin were obtained and cut into 5-mm^2 explants. Two explants were placed, dermal side down, on a 35-mm Petri dish (Falcon), allowed to adhere by drying for 15 min and then covered with 2 ml of culture medium. The culture medium, which was changed weekly, consisted of Eagle's minimum essential medium (Gibco Laboratories, Grand Island, New York) with 10% heat-inactivated fetal calf serum (Gibco Laboratories), penicillin (100 units per ml), streptomycin (100 units per ml), amphotericin B (0.25 mcg per ml), and 0.075% $NaHCO_3$. Cultures were maintained at 37°C in a humidified incubator in 5% CO_2 in air.

Langerhans Cell Identification

Explants derived from 5 surgical specimens were examined serially for the presence of LCs on days 0, 2, and 5 and at weeks 1, 2, and 4 after having been placed in culture. Each explant was removed from the culture plate and examined as a whole mount of epidermis. Separation of epidermis from the underlying dermis was accomplished by incubation in EDTA at 37°C following the method of Scaletta and MacCallum [24].

Epidermal outgrowths from 3 surgical specimens were examined at weeks 1, 2, 3, and 4 for the presence of LCs. Outgrowths were stained within the Petri dish.

Langerhans cells were identified by 3 techniques: ATPase histochemistry and direct immunofluorescence demonstrating either HLA-DR or OKT-6 [25] surface membrane antigens.

ATPase histochemistry: Tissue was fixed in 4% formaldehyde with cacodylic acid buffer and stained for nucleoside triphosphatase according to the method of MacKenzie and Squier [26]. Explants were dehydrated through graded alcohols, followed by xylene, and mounted basal layer up with Permount (Fisher Scientific Co., Fair Lawn, New Jersey).

Direct immunofluorescence demonstrating HLA-DR and OKT-6 surface membrane antigens: Explants were stained using a technique modified from Nordlund and Ackles [27]. Briefly, following acetone fixation, epidermal whole mounts were incubated overnight at 4°C with 100 μl of either a 1:30 dilution of a monoclonal antibody to HLA-DR antigens (L243, a gift of R. Levy) [28] or 100 μl of a 1:100 dilution of a monoclonal antibody to the T6 surface membrane antigen (OKT-6, Ortho Pharmaceutical Corp., Raritan, New Jersey). Specimens were washed in PBS, then incubated at room temperature with a 1:10 dilution of fluoresceinated goat antimouse IgG (Meloy Laboratories, Inc., Springfield, Virginia). Explants were then examined with a Leitz Orthoplan fluorescence microscope equipped with epi-illumination (E. Leitz, Inc., Rockleigh, New Jersey).

Epidermal outgrowths were stained both with and without the central explant in place. Other than acetic acid (0.1%) in 95% ethanol fixation, incubation times and dilutions of reagents were identical to those used for explants. However, it was necessary to use 1.0 cc of each reagent to allow adequate coverage of the outgrowths within the culture plate. Epidermal outgrowths were examined for stained cells using a Leitz Diavert microscope equipped with a Ploemopak 2 fluorescence vertical illuminator (E. Leitz, Inc.).

Quantitation of Langerhans Cells in Explants

Langerhans cells were quantified in the explants by 3 methods. (1) The *percentage of explant surface* staining for LCs was determined by scanning 5 or more low-power (200×) microscopic fields on each specimen. A value of 0%, 50%, or 100% was assigned to each field based on the proportion of the area containing positively stained cells. A percentage for the entire specimen was calculated from an average of these

numbers. (2) *Maximum concentrations* of LCs were obtained from the mean values of 4 high-power microscopic fields (400×) with the greatest number of LCs. The presence of a positively stained cell body was used as the criterion by which cells were counted. (3) The *total tissue density* of LCs was determined for each specimen from the product of the percentage of explant surface staining for LCs and the maximum concentration of LCs.

Quantitation of Langerhans Cells in the Outgrowth

Langerhans cells were quantified in the outgrowth by counting the total number of cells staining within the outgrowth beyond 0.3 mm from the edge of the explant.

RESULTS

Epithelial Morphology of Human Explants

The morphologic characteristics of the explant epithelium using this method of organ culture have been described in detail [29]. Briefly, the upper epidermal layers degenerated in the first several days of culture leaving a viable basal cell layer. In subsequent weeks, a secondary epithelium developed, consisting of 2–3 layers of flattened basaloid cells surrounded by several cornified layers of epithelium.

Morphology of Langerhans Cells in Human Skin Explants

Prior to culture, LCs from each surgical specimen exhibited the typical dendritic morphology as identified by ATPase histochemistry (Fig 1) and by direct immunofluorescence with monoclonal antibodies to HLA-DR (Fig 2) or OKT-6 (Fig 3) surface membrane antigens. Changes in this normal LC configuration became apparent within the first few days in culture. By day 2, the normally homogeneous HLA-DR membrane immunofluorescence appeared discontinuous and clumped (Fig 4). Within the next 2–3 days, ATPase- and immunofluorescence-positive material could be observed to outline many of the other epidermal cells in culture as if positively staining material had been deposited within or remained in the intercellular space (Fig 5). Both of these changes were seen primarily in specimens taken early in the culture period.

Langerhans cells also lost their typical dendritic configuration while in culture (Fig 6). Although some cells assumed this rounded shape early in culture, it was only after the first week that the majority of positively stained cells did so. This rounded form typified LCs over the remaining weeks of the culture period. The presence of a few dendrites and the distribution in the tissue were sufficiently similar to make positively stained cells easily identified as LCs, thereby excluding the possibility that HLA-DR, OKT-6, or ATPase surface membrane markers were being expressed by other populations of epidermal cells.

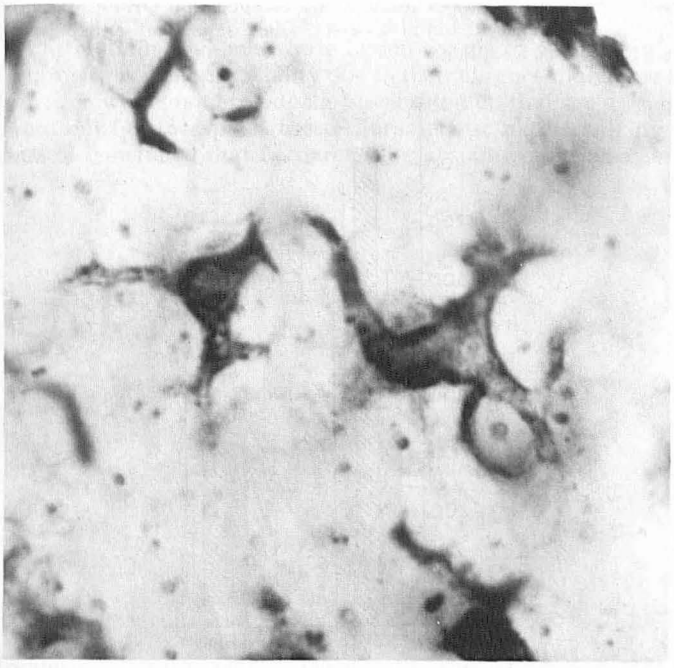

FIG 1. Normal appearance of ATPase-positive dendritic cells in a whole mount of epidermis prior to organ culture. × 400.

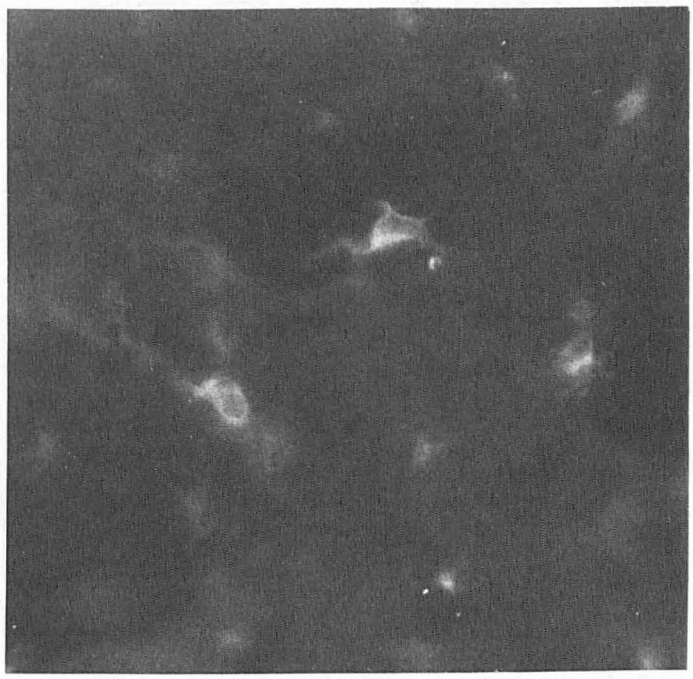

FIG 2. Normal appearance of dendritic cells in a whole mount of epidermis prior to organ culture as demonstrated by direct immunofluorescence of HLA-DR antigens. × 250.

FIG 3. Normal appearance of dendritic cells in a whole mount of epidermis prior to organ culture as demonstrated by direct immunofluorescence of OKT-6 antigens. × 250.

Quantitative Changes in Langerhans Cells in Human Skin Explants

Even before culture, LCs were distributed unevenly over the tissue surface. At that time the percentage of explant surface

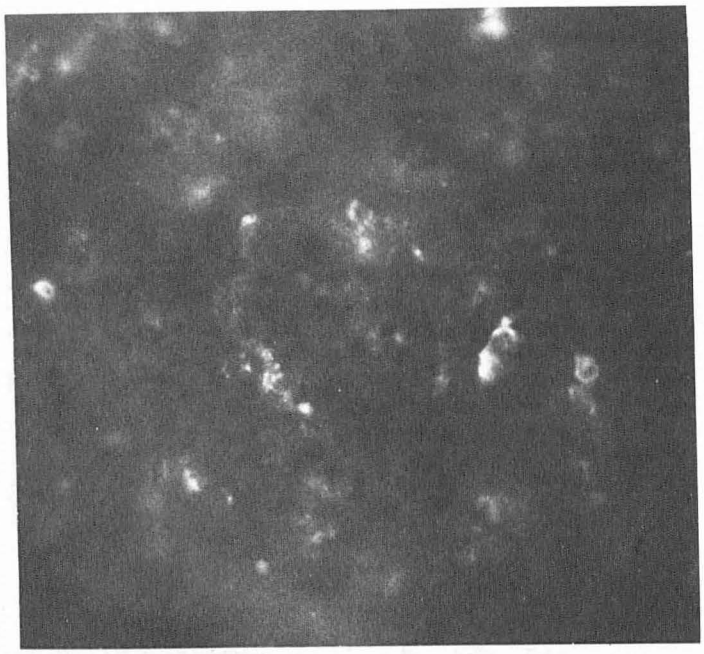

FIG 4. Discontinuous and clumped appearance of LC surface membrane HLA-DR immunofluorescence in a 3-day explant. × 250.

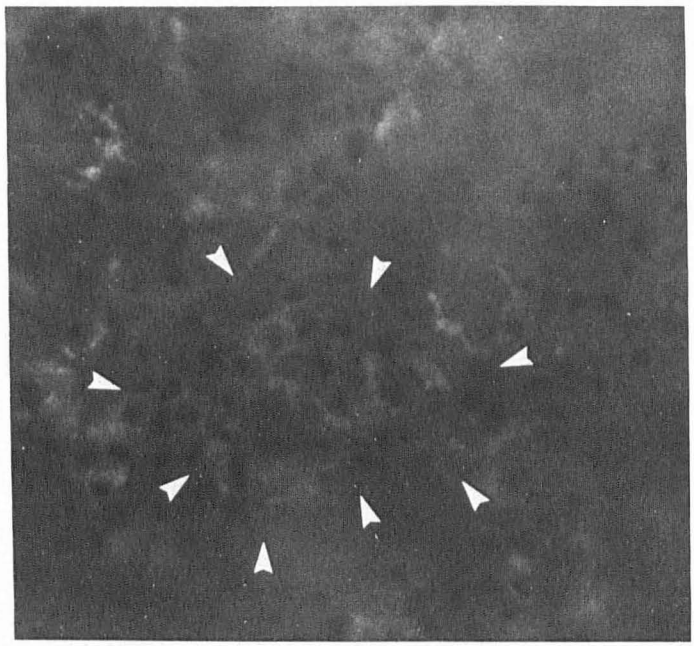

FIG 5. Deposition of HLA-DR immunofluorescence positive material in the intercellular space of an explant, typical of the staining pattern seen at day 5. × 250.

staining for LCs varied from 60% with the OKT-6 reagent to 81% with ATPase histochemistry to 84% with the HLA-DR monoclonal antibody (Fig 7). Prolonged culture accentuated this phenomenon. By the end of 4 weeks in culture only 11, 24, or 56% of the explant surface stained with the OKT-6, ATPase, or HLA-DR markers, respectively.

The maximum concentrations of LCs declined in a parallel manner to that of the percent of explant surface staining for LCs (Fig 8). Before the skin was explanted, there were means of 640 cells/mm^2 (OKT-6), 830 cells/mm^2 (ATPase), and 540 cells/mm^2 (HLA-DR) in the 5 surgical specimens. After 4 weeks of culture only 125, 280, and 380 cells/mm^2 could be identified using the same 3 techniques.

There was also a progressive reduction in the total tissue density, a parameter estimating all of the positively staining

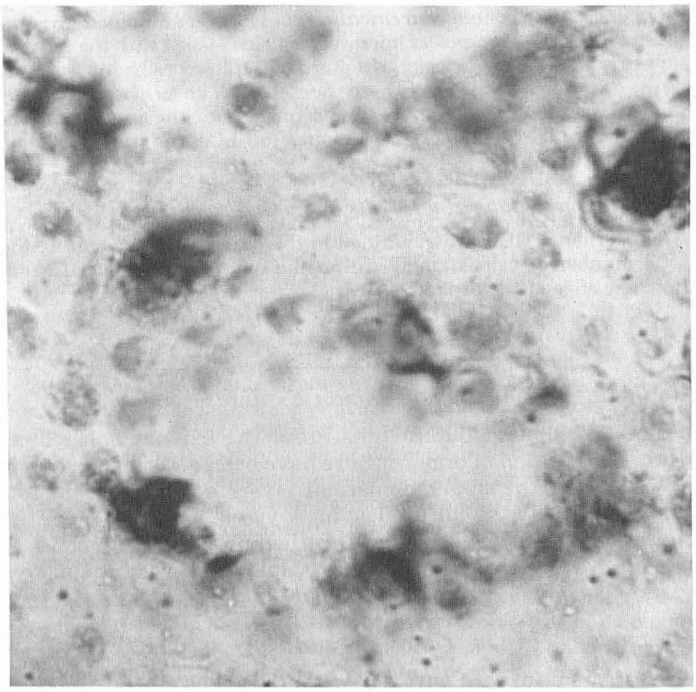

FIG 6. Rounded appearance of ATPase-positive cells in culture. By day 7 most LCs had assumed this configuration. × 400.

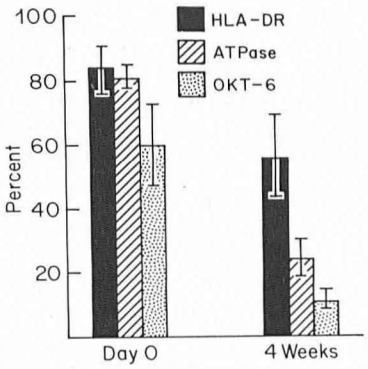

FIG 7. Percentage of explant surface staining for LCs with ATPase histochemistry, HLA-DR immunofluorescence, and OKT-6 immunofluorescence at day 0 and at 4 weeks. The results represent the mean ± SEM of 4 or 5 explants.

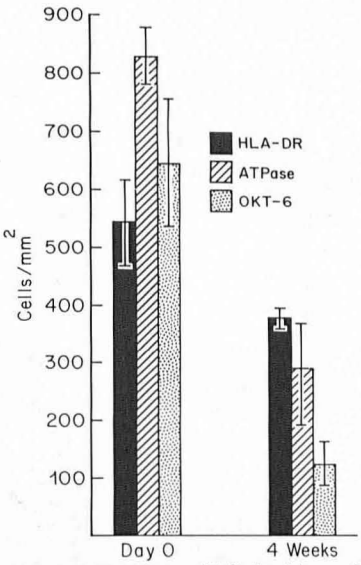

FIG 8. Maximum concentrations of LCs in skin explants as identified by ATPase histochemistry, HLA-DR immunofluorescence, and OKT-6 immunofluorescence at day 0 and at 4 weeks. The results represent the mean ± SEM of 4 or 5 explants.

cells in the specimen (Fig 9). The OKT-6 antigen was the least persistent surface membrane marker examined, falling from 410 cells/mm^2 prior to, to 15 cells/mm^2 at the end of, the culture period. This decline in the number of OKT-6 positive cells became statistically significant ($p = 0.012$) by day 14, and this persisted through day 28. The ATPase surface enzyme marker was of intermediate sensitivity in organ culture. The total tissue density of ATPase-positive cells at day 0 was 675 cells/mm^2. After 5 days in culture there was a statistically significant loss of ATPase-positive cells ($p = 0.002$), and at 4 weeks only 90 ATPase-positive cells/mm^2 could be identified. The HLA-DR antigen was most resistant to loss in culture. Of the 475 cells/mm^2 exhibiting that antigen prior to culture, 215 cell/mm^2 continued to do so at the end of the culture period. Only after 28 days was there a statistically significant difference ($p = 0.04$) compared with pre-culture values. Thus, although there was an absolute reduction in the number of positively staining cells within the explants, LCs did persist for the entire period of organ culture (Figs 10, 11).

Langerhans Cells Within the Epidermal Outgrowth

Over the initial 72 hr following explantation, an outgrowth of epidermis arises peripheral to the explant by migration of epidermis from the original explant. Subsequent enlargement of that outgrowth occurs almost wholly by cellular division [30]. This epidermal outgrowth reaches maximum size by 2–3 weeks, and may extend up to 5 mm in each direction from the explant edges. Rare ATPase-, HLA-DR-, and OKT-6-positive cells could be seen at the edge of the outgrowth adjacent to the original explant. However, beyond 0.3 mm from the explant edge only 1 OKT-6-positive cell was seen in the 11 outgrowths stained (Table I). Two areas of ATPase-positive material resembling cells were noted in one outgrowth. No HLA-DR-positive cells were ever present beyond those contiguous with the explant.

During the staining procedure the epidermal outgrowth remained attached to the Petri dish. To exclude the possibility that the failure to identify LCs in that area resulted from incomplete penetration of reagents, the following positive control was used. Human serum containing antinuclear antibodies was incubated with the epidermal outgrowth as a substrate and then developed with a fluoresceinated rabbit antihuman IgG. Since the nuclei stained positively with this procedure, failure to identify LCs within the epidermal outgrowth was not due to an inability of reagents to penetrate into that tissue.

The inability to demonstrate LCs in the major portion of the outgrowth is in all probability due to their absence in that area; however, we cannot exclude the possibility that they are present there but fail to express these characteristic markers. It may thus be concluded that LCs are either absent from the epidermal outgrowth or that their phenotypic markers are profoundly altered.

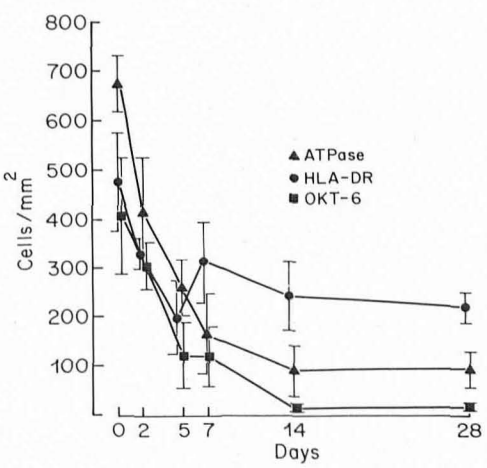

FIG 9. Total tissue density of ATPase-positive, HLA-DR-positive, and OKT-6-positive LCs in skin explants. The results represent the mean of 4 or 5 explants.

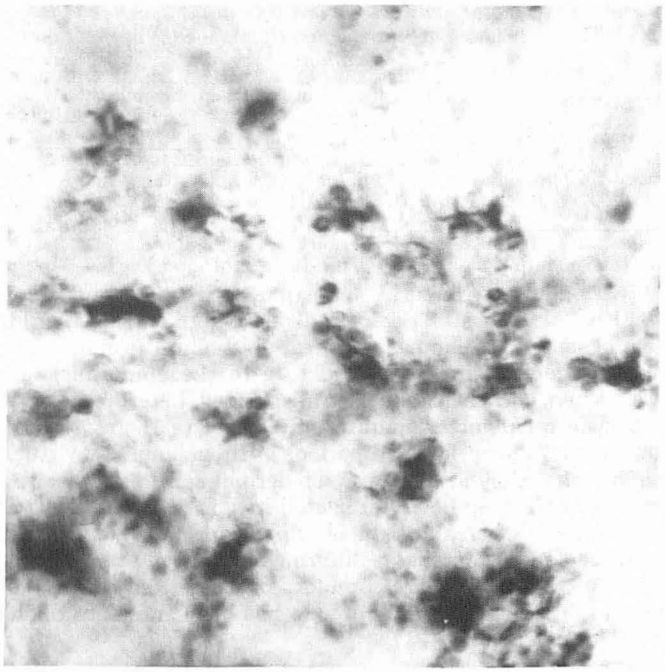

FIG 10. ATPase-positive cells in an explant after 4 weeks in culture. × 200.

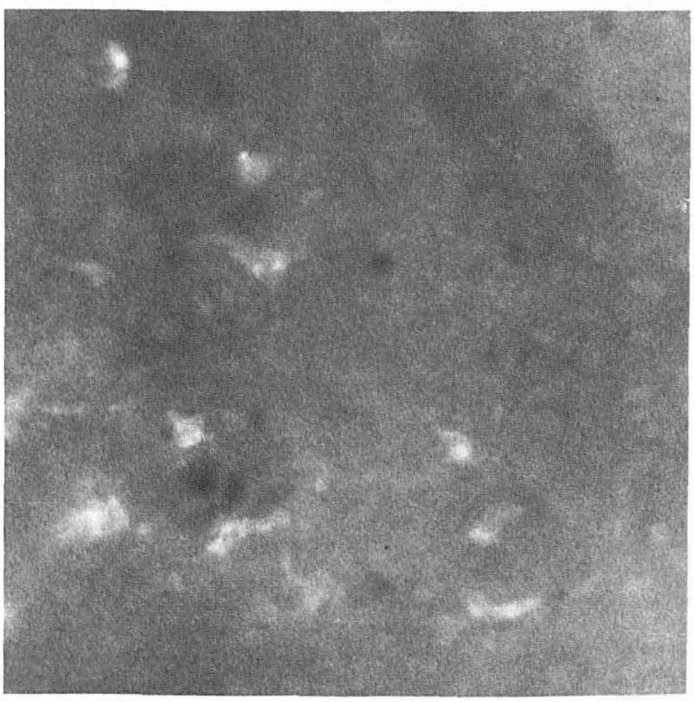

FIG 11. HLA-DR-positive cells in an explant after 4 weeks in culture. × 250.

DISCUSSION

When human skin was placed in organ culture, LCs remained within the original explant and apparently failed to populate the epidermal outgrowth. As identified by ATPase histochemistry and by immunofluorescence with monoclonal anti-HLA-DR and -OKT-6 antibodies, their typical dendritic configuration was rapidly lost, and their normally homogeneous pattern of cell surface molecules was altered. Moreover, in organ culture, to a varying degree, these cells failed to express the ATPase, HLA-DR, and OKT-6 surface membrane markers by which they were identified.

TABLE I. *Total numbers of positively staining cells in the epithelium outgrowth beyond 0.3 mm from the edge of the original explant*

Staining technique	Number of outgrowths stained	Total number of positively staining cells beyond 0.3 mm from explant edge
ATPase	11	2
HLA-DR	11	0
OKT-6	11	1

It has been shown that LCs contribute to the immunogenicity of epithelial allografts. Streilein, Toews, and Bergstresser [18] have observed that murine corneal epithelium (a nonkeratinizing epithelium similar in structure to the epidermis) lacks LCs. When corneal tissue is transplanted heterotopically to allogeneic recipients disparate only for class II antigens, the grafts survive for prolonged periods of time. Thus, by virtue of the fact that they are the only epidermal cell to synthesize Ia antigens, LCs have been implicated in skin allograft rejection. Furthermore, when allografts obtained from tape-stripped skin are transplanted to animals differing only in the I region of the major histocompatibility complex, prolonged survival is observed [19]. Tape-stripping of skin has been shown to deplete the epidermis of LCs [31].

The extent to which LCs are required to process and/or present non-class II transplantation antigens is not fully established. H-2K region differences alone have been shown to be sufficient to initiate allograft rejection in the mouse when non-LC-bearing corneal tissue is used for grafting [18]. Steinmuller has reached similar conclusions using skin allografts differing at minor transplantation antigen loci [32].

Organ culture of other tissues, such as the thyroid [20], pancreas [21], and ovary [22] prolongs allograft survival presumably through the loss of Ia-bearing, antigen-presenting cells. In this study, we have shown that prolonged organ culture fails to deplete human skin explants of LCs, the antigen-presenting cells of the epidermis. One would therefore predict that allografts from tissue prepared in this manner would immunize the recipient against Ia antigens and would be rejected. If these findings in human tissue can be extrapolated to the murine system, then evidence in support of this supposition can be obtained from the work of Ninneman and Good [33] who found no prolongation of allograft survival after organ culture of murine skin. We have, however, shown that the epidermal outgrowth is in all probability devoid of LCs, and it may therefore be a suitable source of tissue to test the hypothesis that LCs are important in skin allograft rejection.

The findings utilizing organ culture of skin contrast with those of epidermal cell culture [34,35]. Cells obtained from epidermal cell culture after 1–2 weeks in culture fail to stimulate allogeneic lymphocytes in the mixed epidermal cell-lymphocyte reaction. Moreover, the loss of stimulatory capacity correlates with the decrement in ATPase-positive and HLA-DR-positive cells. Although we have not tested the capacity of the skin placed in organ culture to stimulate allogeneic lymphocytes, ATPase-, OKT-6-, and HLA-DR-positive cells persist for longer than 4 weeks in this type of in vitro system. The fact that LCs do persist for prolonged periods of time in organ culture suggests that this type of in vitro system may be utilized to explore those factors that have a local influence on LC survival and/or modulate the expression of its surface membrane markers.

Two alternatives may be proposed to explain the preferential location of ATPase-, HLA-DR-, and OKT-6-positive LCs within the explant rather than in the epidermal outgrowth. It is known that LCs divide infrequently [36]. Expansion of the epidermal outgrowth after the initial 3 days in culture occurs almost exclusively by cellular division. Thus, one might postulate that once situated within the epidermis, LCs fail to migrate to other areas of the epidermis lacking LCs, and that any replication of LCs that occurs is insufficient to populate the epidermal outgrowth. Alternatively, LCs may require the presence of adjacent dermis or a factor derived from the dermis for survival or for expression of these cell surface markers. Either one of these hypotheses could explain the observation that occasional LCs are found in areas of the outgrowth adjacent to the explant.

Organ culture of skin may thus provide both a means to examine the role of LCs in skin allograft rejection and a method to isolate those factors that locally affect LCs.

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MINUTES

General Assembly of Members of the 12th Annual Meeting of the European Society for Dermatological Research

Rai-Congrescentrum, Amsterdam, April 5, 1982

H. HÖNIGSMANN, SECRETARY

Present: Seventy-six active and senior members.

Presidential Address: The President, M. Greaves, first paid tribute to the death of Professor G. Kalsbeek from Utrecht by observing two minutes' silence which was respected by the members. He then sounded a gentle note of caution to the Society that, after 12 years, it had not increased its impact. Although the number of applicants had risen, this was a poor measure of the health of the Society, and its success should depend on the quality of the science being transacted during its proceedings. He pointed out that the quality of abstracts submitted to the Programme Committee was variable this year and expressed concern about some stagnation in creativity. He felt unhappy that there had been no real involvement with nondermatological investigators in past meetings; this year, however, the Programme Committee had taken a small step by inviting several distinguished nondermatologists.

Minutes of the 1981 General Assembly: These were approved without dissent.

Report of the Secretary: H. Hönigsmann reported on the present state of membership. Until the deadline, November 30, 1981, 40 applications were recommended by the Board. As of March 31, 1982, the ESDR had 400 members: 338 active, 52 senior, and 10 supporting.

The Secretary also reported on the negotiations with Syntex, originally initiated by Malcolm Greaves, which had resulted in regular annual support of US $5,000 for the ESDR secretariat. This grant covers the salary of a part-time secretary.

The Newsletter, now edited by the Secretary, had received disappointingly little attention from the membership. It was established as a source of information and as a forum for the exchange of ideas. The Secretary pointed out that he has tried to encourage people to contribute to the Newsletter and urged organizers of ESDR-sponsored meetings and symposia to send short reports for publication. He stressed that the input had been very poor and this was reflected by the contents of the Newsletter which consisted mainly of organizational items.

In order to encourage younger investigators to attend the Annual Meeting, graded registration fees have been fixed. For future meetings, it is planned to pose travel support for residents who are presenting a paper. In addition, the Board has decided to subsidize a limited number of individuals from eastern European countries with currency difficulties. The national Dermatological Societies have been informed of this decision.

Effective June 15, 1982, Dr. Howard P. Baden from Harvard Medical School, Boston, will be the Editor of the JID. As the ESDR members of the Editorial Board, he has appointed Dr. Charles Lapière as European Chief Editor, and Drs. Rona MacKie and Georg Stingl as coeditors. Dr. Lapière will attend future ESDR Board meetings as a coopted member.

The Secretary thanked Drs. Frenk, Schaefer, and van Joost for their help in amending the statutes.

Report of the Treasurer: W. van Vloten reported on the expenses and income of the last year. The credit balance stood at Fl. 31,636.46 (savings account - Fl. 80,000.00). He pointed out that, due to economic problems, there might have to be an increase in the subscription fee. The Treasurer's report was accepted without dissent.

Report of the Programme Committee (M. Greaves, Chairman, G. Plewig, A. Giannetti): For the first time, a central theme was chosen for the Annual Meeting: The Pharmacology of Inflammation. The Committee would, however, value written or verbal comments from members on whether to continue with this practice. Of the abstracts received for the 1982 Meeting, approximately 50% had been accepted. M. Greaves further commented on the fact that some posters, which had been accepted for presentation, had already been presented two days previously at the Meeting of the Society for Cutaneous Ultrastructive Research. Although the rules state only that material must not be presented before submission, this practice appeared nevertheless highly undesirable.

Report of the Editor of The Journal of Investigative Dermatology: M. Greaves welcomed both officers of the forthcoming Board of the JID, Howard P. Baden and Charles Lapière, to the Meeting and wished them every success for the future.

G. Plewig reported on Ruth Freinkel's annual report and quoted two letters, the Editorial Board Meeting note of December 1981 and the Editorial Report. According to the financial position of the JID, an increase from $40 to $45 in the subscription would be necessary to adjust to inflation. In order to publish 50% of unsolicited manuscripts submitted to the Journal, the JID would require an additional 100 pages in 1983. This could be financed as follows: 1) increase in the subscription rate, 2) charging a submission fee, or 3) charging a fee for publication.

In a lively debate, the Membership strongly opposed a page charge.